Complete Summary

GUIDELINE TITLE

Management of single brain metastases.

BIBLIOGRAPHIC SOURCE(S)

Neuro-oncology Disease Site Group. Mintz AP, Perry J, Cairncross G, Chambers A. Management of single brain metastases [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2004 Aug 17. 25 p. (Practice guideline report; no. 9-1). [50 references]

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

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SCOPE

DISEASE/CONDITION(S)

Confirmed cancer and a suspected single brain metastasis

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Diagnosis
Management
Treatment

CLINICAL SPECIALTY

Neurological Surgery
Oncology
Radiation Oncology
Surgery

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

Diagnosis

- To evaluate the optimal imaging modality for the diagnosis of single brain metastases
- To evaluate when stereotactic biopsy should be used to establish tissue diagnosis of single brain metastases prior to the initiation of other treatments

Management

- To evaluate the optimal dose of whole brain radiation therapy for patients with confirmed single brain metastases
- To evaluate if patients with confirmed single brain metastases should have surgical resection prior to radiation therapy
- To evaluate the role of stereotactic radiosurgery in the management of patients with single brain metastases
- To evaluate the role of chemotherapy in patients with single brain metastases

TARGET POPULATION

Adults with confirmed cancer and a suspected single brain metastasis

Note: This practice guideline does not apply to patients with metastatic lymphoma, small cell lung cancer, germ cell tumour, leukemia, or sarcoma.

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Contrast-enhanced, standard-dose, and high-dose magnetic resonance imaging (MRI)
2. High and standard-dose computed tomography (CT)
3. Standard and high-dose gadolinium MRI
4. High-dose contrast-enhanced MRI

5. Stereotactic biopsy

Management/Treatment

1. Whole brain radiation therapy (WBRT)
2. Surgery plus radiation therapy versus radiation alone
3. Surgery plus radiation therapy versus surgery alone
4. Stereotactic radiosurgery (SRS)
5. Stereotactic radiosurgery plus WBRT
6. Chemotherapy
    - Cyclophosphamide, fluorouracil and prednisone (CFP) or cyclophosphamide, fluorouracil and prednisone plus methotrexate and vincristine
    - WBRT plus platinum-based chemotherapy versus WBRT alone
    - Chemotherapy plus radiation therapy
    - Temozolomide

MAJOR OUTCOMES CONSIDERED

- Survival
- Quality of life
- Morbidity of interventions
- Local control of disease

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

MEDLINE (1966 through June 2004), EMBASE (1980 through week 25, 2004), CANCERLIT (1983 through October 2002), and the Cochrane Library (2004, Issue 2) databases were searched with no language restrictions. "Brain neoplasms" (Medical Subject Heading [MeSH]), "brain adj2 metastas#s" (text word), "cerebral adj2 metastas#s" (text word) or "metastatic brain" were combined with "single" or "solitary" used as text words. These search terms were then combined with "radiotherapy, adjuvant" (MeSH), "combined modality therapy" (MeSH), "radiosurgery" (MeSH), "chemotherapy, adjuvant" (MeSH), "tomography, x-ray computed" (MeSH), "magnetic resonance imaging" (MeSH), "diagnostic imaging" (MeSH), and the following phrases used as text words: "surgery", "radiation", "radiotherapy", "chemotherapy", "computed tomography", "contrast dose", and "contrast enhancement". These terms were then combined with the search terms for the following study designs: practice guidelines, meta-analyses, randomized controlled trials, clinical trials, cohort studies, and retrospective studies. In addition, the proceedings of major conferences, including the annual meetings of the American Society of Clinical Oncology (1997 to 2004) and the American

Society for Therapeutic Radiology and Oncology (1998 to 2003), were also searched for reports of new or ongoing trials. Relevant articles and abstracts were selected and reviewed and the reference lists from these sources were searched for additional trials.

Inclusion Criteria

Articles were selected for inclusion in this practice guideline if they were fully published reports or published abstracts of:

1. Meta-analyses, systematic reviews, and randomized trials addressing specific guideline questions. If none of these study types were available, retrospective reviews and prospective case series were eligible for inclusion.
2. Outcomes of interest were survival, quality of life, morbidity of interventions, and local control of disease. Studies had to report data on at least one of these outcomes to be eligible for inclusion.

Exclusion Criteria

1. Letters and editorials were not considered.
2. Papers published in a language other than English were not considered.
3. Articles regarding patients with metastatic lymphoma, small cell lung cancer, germ cell tumour, leukemia, and sarcoma were excluded.

NUMBER OF SOURCE DOCUMENTS

13 randomized controlled trials, 9 case series, 11 retrospective reviews, 2 cohort studies, and 7 prospective phase II studies were reviewed.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Individual Patient Data
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

An analysis of individual patient data from the three randomized controlled trials (RCTs) that compared surgery plus radiation therapy to radiation therapy alone was conducted. The patient mortality data had four common and comparable variables: treatment allocation (surgery plus radiation versus radiation alone), age ($\leq$60 versus >60), primary site of cancer (lung versus other), extent of disease (limited versus extensive). Mortality data was converted to days to allow for the

production of Kaplan-Meier survival curves. The survival curves were generated and compared using a modified Gehan-Wilcoxon test. Overall median survival was calculated. Main effects Cox modeling was utilized to generate hazard ratios on the above four variables, which were chosen a priori to the analysis.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The Disease Site Group (DSG) decided to limit the target population for the guideline to exclude patients with metastatic lymphoma, small cell lung cancer, germ cell tumour, leukemia, or sarcoma because these are radiosensitive primary tumours, which respond differently than other tumours to radiation therapy.

After reviewing the guideline report, the DSG members discussed the role of postoperative whole brain radiation therapy (WBRT) in terms increasing survival. Other issues addressed in discussion of the guideline included computed tomography (CT) versus magnetic resonance imaging (MRI) (including contrast dosage), evidence surrounding stereotactic biopsy, stereotactic radiosurgery (SRS), and chemotherapy. The Neuro-oncology DSG drafted recommendations based on the evidence. The DSG attempted to draft recommendations based on the perceived practice variations within Ontario.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner feedback was obtained through a mailed survey of 62 practitioners in Ontario (11 medical oncologists, 15 radiation oncologists, 26 surgeons, seven neurologists, one hematologist, and two pathologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on June 4, 2003. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package

mailed again). The Neuro-oncology Disease Site Group (DSG) reviewed the results of the survey.

The practice guideline report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Eight of 12 members of the PGCC returned ballots. One member indicated that he was also a member of the Neuro-oncology DSG and as such was not eligible to review the practice guideline report. Four PGCC members approved the practice guideline report as written, one member approved the guideline and provided suggestions for consideration by the Neuro-oncology DSG, and two members approved the guideline conditional on the Neuro-oncology DSG addressing specific concerns.

Final approval of the practice guideline report is obtained from the PGCC.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Contrast-enhanced computerized tomography is the standard diagnostic test for individuals suspected of intracranial primary or metastatic cancer. In those individuals in whom there appears to be a solitary metastasis and in whom the primary tumour site is controlled or unknown, high-dose contrast imaging studies are appropriate. This may be accomplished with iodinated contrast (100 mL of current nonionic contrast at 30mg iodine [I]/mL) and a repeat computerized tomographic scan. Alternatively, high-dose contrast gadolinium enhanced magnetic resonance images may be used as they have been demonstrated to increase the sensitivity in detecting smaller lesions.

  Data from two randomized control trials report that the false positive rate for magnetic resonance imaging in determining the presence of brain metastases ranges from 2% to 11%.

- Stereotactic biopsies should be used if a solitary lesion with characteristics of a cancer is seen with no known primary to establish tissue diagnosis prior to other treatments. Patients should be encouraged to participate in clinical trials of stereotactic biopsy.
- Postoperative whole brain radiotherapy should be considered to reduce the risk of tumour recurrence for patients who have undergone resection of a single brain metastasis. The optimal dose and fractionation schedule for whole brain radiation therapy is 3,000 cGy in 10 fractions or 2,000 cGy in five fractions.
- Surgical excision should be considered for patients with good performance status, minimal or no evidence of extracranial disease, and a surgically accessible single brain metastasis amenable to complete excision. Since treatment in this disease is considered palliative, invasive local treatments must be individualized. Patients with lesions requiring emergency decompression due to intracranial hypertension were excluded from the randomized control trials and should be considered surgical candidates.
- There are insufficient data to recommend the use of stereotactic radiosurgery as an alternative to surgical excision.

- Insufficient data exist regarding chemotherapy alone to extrapolate these findings to patients with single brain metastases where alternate treatment modalities exist.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials, case series, retrospective reviews, cohort studies, and prospective phase II studies.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate diagnosis and management of single brain metastases

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- 3,000 cGy in 10 fractions is the standard management of patients with single brain metastases in the United States and is usually the standard arm in randomized studies of radiation in patients with brain metastases. It is correct that, based solely on evidence, there is no reason to choose 3,000 cGy in 10 fractions over 2,000 cGy in five fractions, but there is a belief that fraction size is important and that 300 cGy a day (3,000/10) will be associated with less long term neurocognitive effects than 400 cGy a day (2,000/5) in the few long-term survivors, which is the reason that many radiation oncologists in Ontario prefer 3,000 cGy in 10 fractions. There is no data to either support or refute this belief; hence, there is no way to resolve it at present. The Neuro-oncology Disease Site Group will update the recommendations as new evidence becomes available.
- Age greater or less than 60 was used in the meta-analysis as a common variable that was statistically significant related to survival. Older age should be used as a guideline for survival with older patients responding less well to surgical intervention. A strict cut-off at 60 is not implied in the decision-making process. Other factors such as performance status and status of the primary disease were also variables that were statistically related to survival. All three of these factors should be considered in deciding which patients should be surgical candidates.

- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the practice guideline is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 Aug 17

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Neuro-oncology Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Neuro-oncology Disease Site Group (DSG) disclosed potential conflict of interest information.

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Management of single brain metastases. Summary. Toronto (ON): Cancer Care Ontario. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on October 6, 2004. The information was verified by the guideline developer on October 20, 2004.

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DISCLAIMER

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Date Modified: 9/25/2006